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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,466	09/10/2004	Marc Ostermeier	56908(71699)	1259

21874 7590 05/29/2008

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
05/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/507,466	OSTERMEIER, MARC	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,8,14 and 45-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7, 8, 14 and 45-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4-24-08 has been entered.

Applicant's amendment filed 4-24-08 has been entered. Claims 1 and 7 have been amended. Claims 6, 9-13 and 15-44 have been canceled. Claims 1-5, 7, 8, 14 and 45-47 are pending and under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 45 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "wherein the inserting randomly comprises one or more of a method selecting from: nuclease treatment, mechanical shearing, chemical treatment or radiation treatment" in claim 45 is vague and renders the claim indefinite. It is unclear what is treated with one or more of a method selecting from: nuclease treatment, mechanical shearing, chemical treatment or radiation treatment. It is unclear how those treatments correlate to inserting randomly. Claim 47 depends from claim 45 but fails to clarify the indefiniteness.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 45-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 45-47 read on inserting randomly comprises one or more of a method selected from nuclease treatment, such as 3' to 5' exonuclease digestion, mechanical sheering, chemical treatment or radiation treatment. The phrase "the inserting randomly comprises one or more of a method selected from nuclease treatment, mechanical sheering, chemical treatment or radiation treatment" is considered new subject matter. The specification fails to provide support for the phrase set forth above. Applicant cites paragraph [0021], [0130], [0140], [1031] and [0177] to support for the amendment filed on 3-29-07, which adds new claims 45-47). Those paragraphs only disclose different nuclease treatment or combination thereof, or other types of treatment including mechanical shearing, chemical treatment, and/or radiation. However, those cited paragraphs fails to provide sufficient support for "one or more of a method selected from nuclease treatment, mechanical sheering, chemical treatment or radiation treatment". The claims encompass treating the insertion sequence or acceptor sequence or both with the recited treatment, however, the specification fails to provide sufficient support for treating the insertion

sequence or acceptor sequence or both with the recited treatment. Thus, the phrase "the inserting randomly comprises one or more of a method selected from nuclease treatment, mechanical sheering, chemical treatment or radiation treatment" is considered new subject matter.

6. Claims 45-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a nucleic acid with nuclease, mechanical shearing, chemicals or radiation for the claimed method in vitro, does not reasonably provide enablement for treating a nucleic acid with nuclease, mechanical shearing, chemicals or radiation for the claimed method in vivo, or for treating any molecule other than nucleic acid with nuclease, mechanical shearing, chemicals or radiation for the claimed method in vitro or in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considered whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirement, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d at 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention with function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raises and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claims 45-47 are directed to a method for assembling a modulatable fusion molecule comprising randomly inserting an insertion sequence into an acceptor sequence to generate a fusion molecule and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, and wherein the fusion molecule comprises a new state, wherein the inserting randomly comprises one or more of a method selected from: nuclease treatment, mechanical shearing, chemical treatment or radiation treatment, or further comprises generating a duplication, deletion, substitution at the insertion site in the acceptor sequence. Claim 47 specifies the nuclease treatment comprises digestion with a 3' to 5' exonuclease.

Claims 45-47 read on inserting any molecule randomly into another molecule and the inserting randomly comprises one or more of a method selected from nuclease treatment, such as 3' to 5' exonuclease digestion, mechanical sheering, chemical treatment or radiation treatment in vitro or in vivo. The specification only discloses treating nucleic acid with nuclease treatment, such as 3' to 5' exonuclease digestion, mechanical sheering, chemical treatment or radiation treatment. The specification discloses randomly lineralizing plasmid pDIMC8-Mal by (1) DNase/Mn2+ digestion followed by polymerase/ligase repair, (2) Si nuclease digestion followed by polymerase/ligase repair, and (3) S1 nuclease digestion (not repaired), and the inserted DNA

(bla) be prepared as linear piece of dsDNA with blunt ends containing only the DNA sequence desired to be inserted (e.g. p. 53).

The specification fails to provide adequate guidance and evidence for how to treat a nucleic acid with nuclease, mechanical shearing, chemicals or radiation for the claimed method in vivo, or how to treat any molecule other than nucleic acid with nuclease, mechanical shearing, chemicals or radiation for the claimed method in vitro or in vivo, or further generating a duplication, deletion, substitution at the insertion site in the acceptor sequence.

The specification fails to provide adequate guidance and evidence for how to treat a nucleic acid, including insertion sequence and acceptor sequence, with nuclease, mechanical shearing, chemicals or radiation in vivo, how to prepare randomly linearized insertion sequence and acceptor sequences with nuclease, mechanical shearing, chemicals or radiation in a cell in vivo and how to perform random insertion of an insertion sequence into an acceptor sequence in vivo. The claims encompass any target cell at numerous different locations in a subject. There are various barriers before a outside agent can reach its target cells, for example, skin cells, muscle cells, layers of dermal cells, blood vessel wall cell membranes, nucleases, proteases and lysosomal degradation within cells, extracellular matrix between cells, and gastrointestinal digestive acids. There is no evidence of record that demonstrates treating a nucleic acid, including insertion sequence and acceptor sequence, with nuclease, mechanical shearing, chemicals or radiation in vivo, and performing random insertion of an insertion sequence into an acceptor sequence in vivo. Absent specific guidance, one skilled in the art at the time of the invention would not know how to practice the full scope of the invention claimed.

The specification fails to provide adequate guidance and evidence for how to treat any molecule other than nucleic acid with nuclease, mechanical shearing, chemicals or radiation for the claimed method in vitro or in vivo, or further generating a duplication, deletion, substitution at the insertion site in the acceptor sequence. It is apparent that the specification only provides an example of preparing random nucleic acid insert and inserting nucleic acid sequence into another nucleic acid sequence. It was well known in the art that the methods of nuclease treatment, mechanical shearing, chemical treatment and radiation treatment are used to fragment a nucleotide sequence into smaller nucleotide sequences. It was well known in the art to insert a nucleotide sequence into another nucleotide sequence by using ligase so as to combine those two sequences. The specification fails to provide specific guidance and evidence for how to insert a sequence, such as a protein sequence, an antibody, a carbohydrate molecule, or any organic compound, into another protein sequence, antibody, carbohydrate molecule, or any organic compound by using nuclease treatment, such as 3' to 5' exonuclease digestion, mechanical sheering, chemical treatment or radiation treatment, or further generating a duplication, deletion, substitution at the insertion site in the acceptor sequence. There is no evidence of record that shows nuclease treatment, such as 3' to 5' exonuclease digestion, mechanical sheering, chemical treatment or radiation treatment can insert a protein sequence, an antibody, a carbohydrate molecule, or any organic compound into an acceptor molecule to generate a fusion molecule. Absent such guidance, one skilled in the art at the time of the invention would not know how to practice the full scope of the invention claimed.

For the reasons set forth above, one skilled in the art at the time of the invention would have to engage in undue experimentation to practice over the full scope of the invention claimed.

This is particularly true based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, the level of one of ordinary skill which is high, the amount of experimentation required, and the breadth of the claims.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 1-5, 7, 8 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Lacatena et al., 1994 (PNAS, Vol. 91, pp. 10521-10525).

Claims 1-5 and 14 are directed to a method for assembling a modulatable fusion molecule comprising randomly inserting an insertion sequence into an acceptor sequence to generate a fusion molecule and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, and wherein the fusion molecule comprises a new state. Claims 2-3 specify the state of the insertion sequence is modulated and in response to a change in the state of the acceptor sequence, respectively. Claims 4-5 specify the state of the acceptor sequence is modulated and in response to a change in the state of the insertion sequence, respectively. Claim 14 specifies the fusion molecule can switch between at

least an active state and a less active state. Claims 7-8 are directed to a method for assembling a fusion molecule comprising inserting an insertion sequence into an acceptor sequence to generate a fusion molecule, generating a duplication, deletion, or substitution at the insertion site in the acceptor sequence, and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, wherein the fusion molecule comprises a new state.

Lacatena teaches using TnphoA, a transposon probe for protein export signals, to generate hubeta2AR-phoA fusion protein in vivo by transposition of TnphoA into the hubeta2AR gene in PUC18. Lacatena examined 23 independent Pho+ hubeta2AR:TnphoA insertions and found 13 different fusion sites in the hubeta2AR molecule. The 13 fusion sites are clustered in the first three transmembrane domains and in the C terminus of the hubeta2AR molecule (e.g. bridging p. 10522-10523). Generation of the hubeta2AR-phoA fusion protein constitutes insertion of an insertion sequence into an acceptor sequence and said insertion couples the state of the insertion sequence to the state of the acceptor sequence. PhoA can be considered as an insertion sequence and the hubeta2AR (human beta2-adrenergic receptor) protein can be considered as an acceptor sequence, which has a deletion, and the insertion is random. Lacatena also teaches fusing the coding region of the hubeta2AR gene to the IPTG-inducible lac promoter (e.g. p. 10522, right column). The IPTG-inducible lac promoter is responsive to IPTG. When IPTG is present, the fusion molecule (lac promoter-hubeta2AR gene) switches state in response to the signal (IPTG). Thus, claims 1-8 and 14 are anticipated by Lacatena.

Applicant argues that the teachings of Lacatena reference do not suggest a method of random insertion of an insertion sequence into an acceptor sequence. The Lacatena reference is a topological analysis of the human beta2 adrenergic receptor in E. coli using hubeta2AR-PhoA fusions to determine the proteins topology and Figure 2 describes gene fusions encoding proteins with various lengths of hubetaAR from the N terminus joined to PhoA at the C terminus. The fusions are between the N-terminal region of human betaAR and C-terminal PhoA (amendment, p. 8-9). This is not found persuasive because of the reasons set forth above and the following reasons. Lacatena teaches random insertion of PhoA (alkaline phosphatase) into hubeta2AR protein by using bacteriophage lamda:TnphoA having a transposon. The transposon can randomly insert into target DNA sequence. Figure 2 of the reference shows various insertion sites of PhoA into hubeta2AR protein from N-terminus to C-terminus. The insertions are not restricted to a particular region of the hubeta2AR protein. Lacatena uses a set of hubeta2AR-PhoA fusion to determine the topology in the bacterial membrane and found that the correct positioning of the N terminus is dependent on the presence of C terminal portions of hubeta2AR. However, it does not mean that generation of various fusion proteins by insertion of PhoA into hubeta2AR protein is not random. Thus, the claims are anticipated by Lacatena.

9. Claims 1-5, 7, 8 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Anderson et al., 2003 (US Patent No. 6,596,485 B2).

Claims 1-5 and 14 are directed to a method for assembling a modulatable fusion molecule comprising randomly inserting an insertion sequence into an acceptor sequence to generate a fusion molecule and selecting a fusion molecule wherein insertion couples the state of the

insertion sequence to the state of the acceptor sequence, and wherein the fusion molecule comprises a new state. Claims 2-3 specify the state of the insertion sequence is modulated and in response to a change in the state of the acceptor sequence, respectively. Claims 4-5 specify the state of the acceptor sequence is modulated and in response to a change in the state of the insertion sequence, respectively. Claim 14 specifies the fusion molecule can switch between at least an active state and a less active state. Claims 7-8 are directed to a method for assembling a fusion molecule comprising inserting an insertion sequence into an acceptor sequence to generate a fusion molecule, generating a duplication, deletion, or substitution at the insertion site in the acceptor sequence, and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, wherein the fusion molecule comprises a new state.

Anderson teaches generating random peptide by chemically synthesizing nucleic acid encoding the random peptide, and the nucleic acid and peptide consists of essentially random nucleotides and amino acids (e.g. column 5, lines 13-28). Anderson teaches fusing random peptide into GFP to generate GFP fusion protein via insertion of nucleic acid. The random peptide is fused to an internal position of the GFP and the peptide can be inserted at virtually any position but preferred positions include insertion at the very tips of loops on the surface of the GFP (e.g. column 17, lines 1-38), and "one or more amino acids of the GFP can be deleted and replaced with the peptide" (e.g. column 17, lines 8-10). The derivative GFP contains at least one amino acid substitution, deletion or insertion that can occur at any residue within the GFP protein (e.g. column 3, lines 28-34). Anderson also teaches the fusion nucleic acids encoding the fusion polypeptide, and expression vector comprising a transcriptional regulatory sequence operably

linked to the nucleic acid encoding the fusion protein, wherein the transcriptional regulatory sequence can be a promoter, such as an inducible promoter, for example Tet regulatory element (e.g. column 18, lines 32-55, column 19, lines 19-27). Generation of the GFP fusion protein constitutes insertion of an insertion sequence into an acceptor sequence and said insertion couples the state of the insertion sequence to the state of the acceptor sequence. The peptide can be considered as an insertion sequence and the GFP can be considered as an acceptor sequence, which can have a deletion, a substitution or insertion. The inducible promoter, such as Tet regulatory element, is responsive to inducer, such as tetracycline. When inducer, such as tetracycline, is present, the fusion molecule (fusion nucleic acid operably linked to the inducible promoter) switches state in response to the signal (the inducer, such as tetracycline). Thus, claims 1-5, 7, 8 and 14 are anticipated by Anderson.

Applicant argues that the insertion of the peptide taught by '485 (Anderson) reference is not random and Figure 1 depicts the temperature factors used to pick some of the loops for internal insertion of random peptides (amendment, p. 9). This is not found persuasive because of the reasons set forth above. Anderson teaches fusing random peptide into GFP to generate GFP fusion protein via insertion of nucleic acid. The random peptide is fused to an internal position of the GFP and the peptide can be inserted at virtually any position. The temperature factor just provide a preferred insertion site, such as loop, but it is not necessarily that the insertion has to occur in the loop. The insertion can be at virtually any position within GFP. Therefore, the insertion of the random peptide to GFP is considered random insertion.

10. Claims 1-5, 7, 8 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Manoil et al., 1990 (Journal of Bacteriology, Vol. 172, No. 2, p. 515-518).

Claims 1-5 and 14 are directed to a method for assembling a modulatable fusion molecule comprising randomly inserting an insertion sequence into an acceptor sequence to generate a fusion molecule and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, and wherein the fusion molecule comprises a new state. Claims 2-3 specify the state of the insertion sequence is modulated and in response to a change in the state of the acceptor sequence, respectively. Claims 4-5 specify the state of the acceptor sequence is modulated and in response to a change in the state of the insertion sequence, respectively. Claim 14 specifies the fusion molecule can switch between at least an active state and a less active state. Claims 7-8 are directed to a method for assembling a fusion molecule comprising inserting an insertion sequence into an acceptor sequence to generate a fusion molecule, generating a duplication, deletion, or substitution at the insertion site in the acceptor sequence, and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, wherein the fusion molecule comprises a new state.

Manoil teaches using a transposon derivative of Tn5 (TnphoA) containing a phoA gene missing its promoter, its translation initiation site, and DNA corresponding to the signal sequence and first five amino acids of the protein, to insert into a gene to generate hybrid proteins. The insertion of TnphoA into a gene (transposon insertion) is random and the fusion gene encoding hybrid proteins with alkaline phosphatase activity are detected as blue colonies on media containing the alkaline phosphatase indicator dye (e.g. p. 515, right column). Generation

of the hybrid proteins constitutes insertion of an insertion sequence into an acceptor sequence and said insertion couples the state of the insertion sequence to the state of the acceptor sequence. The resulting hybrid protein or gene encoding said hybrid protein is a new state. PhoA gene can be considered as an insertion sequence and the target gene can be considered as an acceptor sequence, and the insertion is random. Thus, the claims are anticipated by Manoil.

11. Claims 1-5, 7, 8 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Mountford et al., 1995 (TIG, Vol. 11, No. 5, p. 179-184).

Claims 1-5 and 14 are directed to a method for assembling a modulatable fusion molecule comprising randomly inserting an insertion sequence into an acceptor sequence to generate a fusion molecule and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, and wherein the fusion molecule comprises a new state. Claims 2-3 specify the state of the insertion sequence is modulated and in response to a change in the state of the acceptor sequence, respectively. Claims 4-5 specify the state of the acceptor sequence is modulated and in response to a change in the state of the insertion sequence, respectively. Claim 14 specifies the fusion molecule can switch between at least an active state and a less active state. Claims 7 and 8 are directed to a method for assembling a fusion molecule comprising inserting an insertion sequence into an acceptor sequence to generate a fusion molecule, generating a duplication, deletion, or substitution at the insertion site in the acceptor sequence, and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, and wherein the fusion molecule comprises a new state.

Mountford teaches gene trapping for identifying developmentally regulated genes based on the random integration of a reporter into chromosomal transcription units. Mountford further teaches that IRES-containing gene trap construct pGT1.8Iresbetageo enhances frequency of productive integration as compared to control vector (e.g. p. 182, right column). The gene trap vector is an insertion sequence and the choromosomal transcription units are acceptor sequences. The resulting fusion molecule is a new state. Thus, the claims are anticipated by Mountford.

12. Claims 1-5, 7, 8 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Ong, Christopher, 2005 (US Patent No. 6,867,035 B2).

Claims 1-5 and 14 are directed to a method for assembling a modulatable fusion molecule comprising randomly inserting an insertion sequence into an acceptor sequence to generate a fusion molecule and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, and wherein the fusion molecule comprises a new state. Claims 2-3 specify the state of the insertion sequence is modulated and in response to a change in the state of the acceptor sequence, respectively. Claims 4-5 specify the state of the acceptor sequence is modulated and in response to a change in the state of the insertion sequence, respectively. Claim 14 specifies the fusion molecule can switch between at least an active state and a less active state. Claims 7-8 are directed to a method for assembling a fusion molecule comprising inserting an insertion sequence into an acceptor sequence to generate a fusion molecule, generating a duplication, deletion, or substitution at the insertion site in the acceptor sequence, and selecting a fusion molecule wherein insertion couples the state of the

insertion sequence to the state of the acceptor sequence, wherein the fusion molecule comprises a new state.

Ong teaches preparation of gene trap DNA construct comprising a mutagenic, detectable component containing a IRES linked to a reporter gene and a functional unit comprising a reporter gene under the control of PGK promoter. Transfection of the gene trap construct via electroporation into ES cells results in random integration into ES cell genome by illegitimate recombination. The trap vector not only introduces a molecular tag that permits subsequent cloning and identification, chromosomal localization and placement onto the physical map of the trapped gene, but also generates ES cells bearing mutations in the respective gene (e.g. column 7, lines 8-47). The gene trap DNA construct is an insertion sequence and the ES cell genome is acceptor sequence. The resulting fusion molecule is a new state. Thus, the claims are anticipated by Ong.

13. Claims 1-5, 7, 8 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Heintz et al., 2002 (US Patent No. 6,485,912 B1).

Claims 1-5 and 14 are directed to a method for assembling a modulatable fusion molecule comprising randomly inserting an insertion sequence into an acceptor sequence to generate a fusion molecule and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, and wherein the fusion molecule comprises a new state. Claims 2-3 specify the state of the insertion sequence is modulated and in response to a change in the state of the acceptor sequence, respectively. Claims 4-5 specify the state of the acceptor sequence is modulated and in response to a change in the state of the

insertion sequence, respectively. Claim 14 specifies the fusion molecule can switch between at least an active state and a less active state. Claims 7-8 are directed to a method for assembling a fusion molecule comprising inserting an insertion sequence into an acceptor sequence to generate a fusion molecule, generating a duplication, deletion, or substitution at the insertion site in the acceptor sequence, and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, wherein the fusion molecule comprises a new state.

Heintz teaches gene trapping in bacterial artificial chromosomes (BACs) by using randomized gene trapping having promoter-5' exon element randomly inserted into a BAC via a Tn 10 transposon system. Randomized gene trapping involves the relatively random insertion of a PEU into a BAC mediated transposon system, such as Tn10 or Tn3 (e.g. detailed description text (77), (83)). The gene trap vector is an insertion sequence and the BAC is an acceptor sequence. The resulting fusion molecule is a new state. Thus, the claims are anticipated by Heintz.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1 and 45-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al., 2003 (US Patent No. 6,596,485 B2) in view of Norris, 2006 (US Patent No. 7,135,176).

Claims 1 and 45-47 are directed to a method for assembling a modulatable fusion molecule comprising randomly inserting an insertion sequence into an acceptor sequence to generate a fusion molecule and selecting a fusion molecule wherein insertion couples the state of the insertion sequence to the state of the acceptor sequence, and wherein the fusion molecule comprises a new state, wherein the inserting randomly comprises one or more of a method selected from: nuclease treatment, mechanical shearing, chemical treatment or radiation treatment, or further comprises generating a duplication, deletion, substitution at the insertion site in the acceptor sequence. Claim 47 specifies the nuclease treatment comprises digestion with a 3' to 5' exonuclease.

Anderson teaches generating random peptide by chemically synthesizing nucleic acid encoding the random peptide, and the nucleic acid and peptide consists of essentially random nucleotides and amino acids (e.g. column 5, lines 13-28). Anderson teaches fusing random peptide into GFP to generate GFP fusion protein via insertion of nucleic acid. The random peptide is fused to an internal position of the GFP and the peptide can be inserted at virtually any position but preferred positions include insertion at the very tips of loops on the surface of the GFP (e.g. column 17, lines 1-38), and "one or more amino acids of the GFP can be deleted and replaced with the peptide" (e.g. column 17, lines 8-10). The derivative GFP contains at least one amino acid substitution, deletion or insertion that can occur at any residue within the GFP protein (e.g. column 3, lines 28-34). Anderson also teaches the fusion nucleic acids encoding the fusion

polypeptide, and expression vector comprising a transcriptional regulatory sequence operably linked to the nucleic acid encoding the fusion protein, wherein the transcriptional regulatory sequence can be a promoter, such as an inducible promoter, for example Tet regulatory element (e.g. column 18, lines 32-55, column 19, lines 19-27). Generation of the GFP fusion protein constitutes insertion of an insertion sequence into an acceptor sequence and said insertion couples the state of the insertion sequence to the state of the acceptor sequence. The peptide can be considered as an insertion sequence and the GFP can be considered as an acceptor sequence, which can have a deletion, a substitution or insertion. The inducible promoter, such as Tet regulatory element, is responsive to inducer, such as tetracycline. When inducer, such as tetracycline, is present, the fusion molecule (fusion nucleic acid operably linked to the inducible promoter) switches state in response to the signal (the inducer, such as tetracycline).

Anderson does not specifically teach DNase treatment or 3' to 5' exonuclease treatment.

Norris teaches random cloning of lamda.DASH-Bb12 insert by treating purified bacteriophage DNA with DNase I in the presence of Mn2+ and cloned into EcoRV-digested pBluescript II SK(-) (description paragraph (161)).

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to use DNase I to treat a DNA for random cloning because Anderson teaches generating random peptide by chemically synthesizing nucleic acid encoding the random peptide, and insertion of the nucleic acid to nucleic acid encoding GFP, and Norris teaches using DNase I to produce random nucleic acid for random cloning of said nucleic acid into a vector. Both Anderson and Norris teaches producing random nucleic acid sequences with different lengths for cloning. It also would have been obvious for one of ordinary skill in the art to use 3'

to 5' exonuclease to generate different lengths of nucleic acid sequences because it was known in the art that 3' to 5' exonuclease can digest nucleic acid sequence to diverse extent to create different lengths of nucleic acid sequences.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order for random cloning of nucleic acid into a vector as taught by Norris or into a target sequence, such as GFP, as taught by Anderson with reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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